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## Original Article

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# Assessment of the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia and neuropathic pain. A pilot study

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### Summary

**Background:** Allodynia is a common and disabling symptom in many patients with neuropathic pain. Whereas quantification of pain mostly depends on subjective pain reports, allodynia can also be measured objectively with quantitative sensory testing. In this pilot study, we investigated the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia as a consequence of a neuropathic pain syndrome, by means of correlating subjective pain scores with pain thresholds obtained with quantitative sensory testing. **Methods:** During a 4-week trial, we administered a cannabis extract to 17 patients with allodynia. We quantified the severity of the allodynia with Von Frey monofilaments before, during and after the patients finished the trial. We also asked the patients to rate their pain on a numeric rating scale at these three moments. **Results:** We found that most of the effect of the cannabis occurred in the last 2 weeks of the trial. In this phase, we observed that the pain thresholds, as measured with Von Frey monofilaments, were inversely correlated with a decrease of the perceived pain intensity. **Conclusion:** These preliminary findings indicate clinical relevance of quantitative sensory testing with Von Frey monofilaments in the quantification of allodynia in patients with neuropathic pain, although confirmation of our data is still required in further studies to position this method of quantitative sensory testing as a valuable tool, for example, in the evaluation of therapeutic interventions for neuropathic pain.

**Keywords:** ALLODYNIA; VON FREY MONOFILAMENTS; QST; NEUROPATHIC PAIN; CANNABIS.

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### Introduction

In many patients with neuropathic pain, the presence of allodynia can be observed [1–3]. Allodynia, defined by the International Association for the Study of Pain (IASP) as pain caused by a stimulus that would not normally evoke pain, can be demonstrated when, for example, lightly rubbing

the affected skin is found to be painful [4]. It is a very disabling physical symptom that frequently co-occurs with hyperalgesia in neuropathic pain syndromes [5,6]. Allodynia can be produced by the action of low threshold A $\beta$ -fibres on an altered central nervous system, but it may also be the consequence of hyperexcitation of nociceptor terminals in the periphery [2]. To determine the exact underlying pathophysiological mechanisms of a patient's allodynia is difficult if not impossible in clinical practice.

As stimulus-independent pain is always subjective; evaluation of the efficacy of analgesic treatment thus depends on a subjective effect size,

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such as a visual analogue scale or numeric rating scale (NRS). This single-dimension subjective scaling does not differentiate between sensory and affective components of pain and addresses the complex nature of the experience as a whole [7,8].

In patients with neuropathic pain, the presence of stimulus-dependent pain, such as allodynia, can be used to evaluate the sensory-discriminative aspects of pain more specifically with quantitative sensory testing (QST). QST can thus be used to evaluate treatment outcome more objectively [9].

Methods for the quantification of stimulus-dependent pain should ideally be simple to execute and yield standardized, validated and reproducible results [10]. Furthermore, the method used should be clinically relevant.

In this pilot study, we investigated the clinical relevance of QST with Von Frey monofilaments in patients suffering from allodynia as a consequence of a neuropathic pain syndrome. Despite its heterogeneity, the clinical symptom allodynia can be quantified within a narrow range of deviation using Von Frey monofilaments [11]. Importantly, QST with Von Frey monofilaments is simple in clinical practice and yields reliable and reproducible results [12,13]. We calculated the correlation between a change in the clinical pain (NRS) and changes in QST responses during a therapeutic intervention (see below). A relation between an improvement of the perceived pain and an increased pain threshold would imply clinical relevance of QST with the monofilaments [9].

In order to achieve intra-individual variation of the intensity of allodynia, we chose to administer a whole-plant cannabis extract to the patients. Cannabis has been shown to improve allodynia and hyperalgesia in animal studies and in one study with experimental neuropathic pain in human beings [14–17]. During a 4-week period, we administered this cannabis extract to 17 patients who suffered from allodynia as a consequence of a unilateral neuropathic pain syndrome.

## Methods

Twenty patients suffering from unilateral neuropathic pain and allodynia participated in this study after giving their informed consent. The study was approved by the Medical Ethics Committee of the University Medical Center Groningen. In these patients, history and physical examination revealed the presence of neuropathic pain and allodynia. Neuropathic pain was diagnosed in all the patients, as there was no tissue damage or nociception that caused the pain, the pain was located in the distribution area of specific nerves or in one or more

dermatomes and there was stimulus-dependent pain. Allodynia was diagnosed when light stroking of the skin was reported as painful on the affected skin.

Patients suffering from polyneuropathy or diabetes mellitus were excluded, as those conditions are associated with hypoesthesia and may subsequently influence the outcome of QST. Drug addiction and psychiatric conditions were also considered as exclusion factors. All patients were Caucasian; Dutch was their native language. The patients continued their usual (analgesic) medication and they and their doctors were asked not to change medication or dosage without consulting one of the members of our research team.

During the first visit (T0), the procedure was explained, QST with Von Frey monofilaments was performed and 3 g of whole-plant cannabis were given in three separate envelopes. The patients were instructed to suspend a tea ball containing 1 g of cannabis for 20 min in 1 L of boiling water. Each night, just before sleeping, the patients drank 200 mL of this tea. They were free to choose whether they preferred the tea warm or cold, and with or without sugar or milk. The remaining tea was preserved in the refrigerator.

Two weeks later (T1), the patient was asked if he had noticed any effects caused by the use of cannabis, either analgesia or side-effects. If the patient had not noticed any effect, the dose was doubled, which meant an extra cup of cannabis-tea to be taken each morning. QST with Von Frey monofilaments was then performed, as well as at the end of the trial 2 weeks later (T2), when the cannabis was discontinued.

## Experimental setting

All patients underwent the measurements in a quiet room with a constant temperature of 20–22°C. Each of the examination was carried out by the same investigator (D.K.). To acclimatize, the patients were present in the room for about 10 min prior to the actual investigation. During this time, the patients were informed about the procedure and the monofilaments were demonstrated to familiarize the patients with the procedure. Subsequently, the patients were investigated while lying comfortably on an examination table.

The patient was asked to point out the skin area where allodynia was perceived as most intense. The punctum maximum of the allodynia was marked with a little square ( $\pm 1 \text{ cm}^2$ ) drawn on the skin. The corresponding spot on the contralateral side of the body was marked similarly. These locations were documented in the patient's medical record for the subsequent measurements 2 and 4 weeks later.

*Subjective pain scores*

The patient was asked to indicate the severity of the pain of that moment on a NRS, which implied that the patient attributed a number to the perceived pain on the affected skin, ranging from 0 (no pain) to 10 (worst pain imaginable).

*Quantitative sensory testing*

A kit consisting of 20 nylon Von Frey monofilaments with increasing diameter of the firm Touch Test<sup>TM</sup> (North Coast Medical, Inc., Morgan Hill, LA, USA) was used for QST. When applied on the skin, monofilaments exert a constant force, as the monofilament bends. This bending reduces measurement outcome artifacts resulting from movement or trembling of the examiner's hand [12].

The monofilaments are calibrated in a logarithmic scale from 0.008 to 300 g (0.08–2943 mN), within a 5% standard deviation (SD). Numbers on each monofilament ranging from 1.65 to 6.65, represent the common logarithm of 10 times the force in milligrams [18].

The monofilaments were applied in increasing thickness (method of limits) on the affected and non-affected side successively, in a randomized sequence, until a pain threshold was detected. The patient was asked to give a clear verbal signal when the stimulus was perceived to be painful. Each monofilament was applied three times, with approximately 10 s between two successive stimuli, to avoid temporal summation [19,20]. Subsequently, the procedure was repeated on the contralateral side.

The monofilament was applied perpendicularly to the skin surface for approximately 2 s, until a bending of 3–5 mm of the monofilament was produced. Patients kept their eyes closed during the investigation to avoid visual feedback concerning the stimuli.

The pain threshold was defined as the logarithmic number on the monofilament in which at least two out of three applications on the affected side resulted in the perception, and subsequent reporting of pain, the so-called 'appearance' threshold [10,21]. Once a pain threshold was reached, QST was stopped. QST of the unaffected side was also performed to obtain baseline values.

The duration of the procedure was 10–15 min. We assumed that no significant loss of attention occurred during this procedure.

*Cannabis extract*

We used standardized whole plant cannabis produced by the firm Maripharma<sup>®</sup> (Rotterdam, The Netherlands). This cannabis has been sterilized for

microbial contamination by means of gamma-irradiation. According to European Pharmacopoeia requirements, the cannabis contains an acceptably small quantity of pesticides and metalloids. In our hospital's department of pharmacy, we measured the tetrahydrocannabinol (THC), cannabinal (CBN) and cannabidiol (CBD) contents in the cannabis (18 samples) and the extract (six samples) by a validated GC–MS method. The mean concentration for THC in the cannabis was  $6\% \pm 0.9\%$  (mean  $\pm$  SD) and in the cannabis-extracts  $1\% \pm 0.2\%$  (mean  $\pm$  SD). CBN and CBD were found neither in the tea bags nor in the extract.

*Statistical analysis*

For the subjective NRS scores as well as the pain thresholds measured with the monofilaments, difference scores were calculated between the various time points (T0, T1 and T2). To investigate the relation between the change in pain thresholds and the change in NRS scores, two-tailed Pearson correlation coefficients were calculated.

For all statistical calculations in this study, *P*-values smaller than 0.05 were considered statistically significant.

**Results***Baseline characteristics of the patients*

Initially, the selected group of patients consisted of six males and 14 females. Three patients were lost to follow-up; one because of the development of oedema in both legs and two other patients because of insufficient ability to co-operate. The data of the remaining 17 patients (five males, 12 females) were analysed. Their mean age was 47.1 yr (range 27–61 yr). The duration of their underlying pain syndromes varied strongly and differed from only a few months to several decades (see Table 1). The neuropathic pain was either the result of surgery [12], trauma [2], stroke [1] or had a (pseudo)-radicular origin [2].

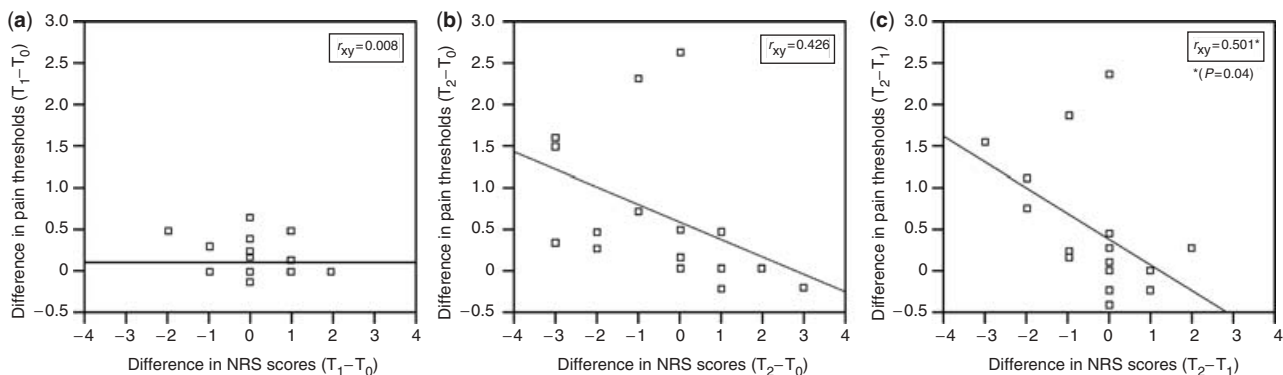
At the time of inclusion, five patients did not use any medication, two patients used a non-steroidal anti-inflammatory drug and 10 patients used a tricyclic antidepressant and/or an antiepileptic drug, sometimes in combination with other analgesic drugs (Table 1).

*Subjective effects and side-effects*

At T1, two of the 17 participating patients indicated to perceive less pain and experienced an improved sense of well-being. In these patients, the dose was not increased. In the remaining 15 patients

**Table 1.** Characteristics of included patients: age, gender, diagnosis, duration of pain and medication use are displayed.

Patient no.	Age (yr)	Sex	Neuropathic pain due to	Duration of pain (months)	Use of medication
1	52	F	Surgery	60	None
2	37	F	Surgery	5	None
3	27	F	Surgery	100	Ibuprofen
4	56	M	(Pseudo)-radicular irritation	22	None
5	54	M	Surgery	72	Gabapentin
6	41	M	Surgery	300	None
7	56	F	Surgery	54	Amitriptyline
8	56	F	Surgery	19	Gabapentin, Tramadol
9	43	F	Surgery	54	Amitriptyline
10	45	F	Stroke following head trauma	25	Gabapentin
11	48	F	Trauma	30	Gabapentin
12	59	F	Surgery	65	Naproxen, tramadol
13	52	F	Surgery	60	Morphine
14	31	F	Surgery	15	Amitriptyline, paracetamol, codeine, gabapentin
15	37	M	Trauma	10	Gabapentin, tramadol
16	46	F	(Pseudo)-radicular irritation	35	Amitriptyline
17	61	M	Surgery	500	None

**Figure 1.**

In the first 2 weeks of the trial no relation between the pain thresholds and subjective pain scores was observed (a). During the last 2 weeks of the trial, the increase in pain threshold correlated significantly with a decreased NRS-score (c). The correlation that was calculated for the whole 4-week period did not reach statistical significance (b). (NRS: numerical rating scale).

the dose was increased, as they described no subjective effect of the cannabis at that moment.

None of the patients that enrolled in this study dropped out because of side-effects. In most patients (15/17), no side-effects occurred at all. However, when side-effects did occur (2/17), they were considered as mild by the participating patients. One patient described a mild transitory redness of the eyes; the other patient had experienced a mild dizziness. Seven patients described an improved sense of well being after completing the trial.

#### *I: Quantitative sensory testing and subjective pain report*

**T1–T0:** For the first 2 weeks of the study, the correlation between the change in pain thresholds

and the change in subjective pain scores was 0.008 ( $P = 0.976$ ), indicating no relation between the measured difference in pain thresholds and the difference in the reported pain.

**T2–T0:** For the whole 4-week period, the correlation between the change in pain thresholds and the change in subjective pain scores was  $-0.426$  ( $P = 0.088$ ).

**T2–T1:** During the last 2 weeks of the study, the correlation between the change in pain thresholds and the change in subjective pain scores was  $-0.501$  ( $P = 0.040$ ) indicating a relation that is statistically significant (see Fig. 1a–c).

On the contralateral, unaffected side, no pain threshold could be determined in 16 of the 17 patients at any time in the study. One patient, with postoperative neuropathic pain as a result of

paramedian abdominal surgery, also experienced the application of thick Von Frey monofilaments on the contralateral healthy skin as painful. She rated her pain of the affected skin to be 10 on the NRS on T0, T1 and T2.

## Discussion

Pain is always subjective [4]. The subjective nature of pain poses a problem on pain researchers and clinicians involved in the treatment of pain on how to quantify pain in order to evaluate therapeutic interventions as objectively as possible. In the case of neuropathic pain, concomitant symptoms such as allodynia and hyperalgesia can be used to quantify the severity of the pain by means of QST [9].

Our pilot study indicated clinical relevance of QST with monofilaments of allodynia in patients suffering from neuropathic pain, since the measured pain threshold is negatively associated with a decrease in the perceived pain intensity. These results are in agreement with other studies in which a relation between QST responses and clinical pain was found [9,22].

Several aspects of this study need further consideration. With respect to terminology, we used the IASP definitions of allodynia and hyperalgesia in this study. We realize that many authors use the term 'punctate hyperalgesia' to indicate the pain following the application of Von Frey monofilaments. However, we did not use the word 'hyperalgesia' since the application of the monofilaments on unaffected skin was not considered painful by the control subjects and in all patients except one. We therefore preferred the term 'allodynia'.

We chose to use a cannabis-extract to influence the severity of the patients' allodynia, as animal studies show that cannabinoids are capable of decreasing the intensity of certain types of stimulus dependant pain, i.e. hyperalgesia and allodynia. In rats, low dose cannabinoids are even capable of reducing allodynia and hyperalgesia, without producing unacceptable side-effects [15,16,23,24]. In human subjects, the topically administered synthetic cannabinoid agonist HU210 attenuated capsaicin-induced touch-evoked allodynia [17]. Of all cannabinoids, the efficacy of ( $\Delta^9$ )-THC against allodynia and hyperalgesia has been studied most extensively. In order to change the patients' allodynia we needed to use a THC-containing cannabis-extract.

Three patients were lost to follow-up during the study. One female patient was excluded during the trial, because of aggravation of pre-existing oedema in both legs that influenced sensory function. She

was referred back to her General Practitioner for diagnostic work-up. Two other patients were excluded due to insufficient co-operation. One of these patients failed to comply with the protocol due to hypochondriasis, while the other patient was unable to produce the cannabis-extract adequately. The latter is an obvious disadvantage in general; although not difficult, the complexity of this procedure can lead to mistakes.

As stated earlier, a relation between an improvement of the clinical pain and an increased pain threshold would imply clinical relevance of QST with the monofilaments. In this study, we found a clear increase of the pain thresholds, however, the decrease of the clinical pain was not statistically significant. Probably, the number of patients that participated in this study was too small, or the quantity of ingested cannabinoids may have been inadequate, to detect this effect. The change in pain thresholds – as measured with the Von Frey monofilaments – and NRS scores, predominantly occurred in the last 2 weeks of the trial (see below). It was in this period (T2–T1) that we found a statistically significant correlation between QST responses and pain report.

Our finding that the change in pain thresholds and pain report mainly occurred in the last 2 weeks of the trial, may be explained by a delayed efficacy of the cannabis. Another possibility that cannot be ruled out is habituation to the testing procedure. However, we regard the latter possibility to be unlikely, since the patients had been familiarized with the testing procedure prior to the actual study. Furthermore, the measurements took place only three times in total, with 2-week intervals. A delayed efficacy of cannabis as an explanation for the change in pain thresholds and pain report is more likely, and may be caused by rapid redistribution of cannabinoids in the body. As a consequence, an effective plasma level of THC is reached only after repeated dosage. Cannabinoids have a long elimination half-life of up to multiple days, due to extensive uptake in the fatty tissues from where slow release takes place [25]. In comparison, many drugs with a known analgesic effect against neuropathic pain, e.g. tricyclic antidepressants, also exert a therapeutic effect with a delayed onset of a few days to several weeks [1]. Finally, the placebo-effect may also account for the change in pain thresholds and pain report, as no control group was included in this study.

In conclusion, we demonstrated that an increased pain threshold correlated significantly with a decreased report of pain in this pilot study. These preliminary findings suggest that QST with Von Frey monofilaments is a clinically relevant method

in patients with allodynia and neuropathic pain, although larger studies are needed for further proof.

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